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EXAMINER
AEDER, SEAN E

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/516,946	PAU ET AL.	
	Examiner	Art Unit	
	SEAN E. AEDER	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-13,19-24 and 27* is/are pending in the application.

4a) Of the above claim(s) *6,7,9,13 and 19-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5, 8, 10-12, 24, and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Amendments and Remarks filed 11/24/08 in response to the Office Action of 5/23/08 are acknowledged and have been entered.

Claims 1, 2, 5-13, 19-24, and 27 are pending.

Claims 6, 7, 9, 13, and 19-23 have been withdrawn.

Claims 1 and 27 have been amended by Applicant.

Claims 1, 2, 5, 8, 10-12, 24, and 27 are currently under examination.

The following Office Action contains NEW GROUNDS of rejections necessitated by amendments.

Rejections Withdrawn

The rejection of claims 1, 2, 5, 10, 12, 24, and 27 under 35 U.S.C. 102(b), as being anticipated by Maurer et al (Digestive Diseases and Sciences, 43(12): 2641-2648), is withdrawn.

The rejection of claims 1 and 11 under 35 U.S.C. 103(a), as being unpatentable over Maurer et al (Digestive Diseases and Sciences, 43(12): 2641-2648) as applied to claim 1 above, and further in view of Aggarwal et al (J Immunol, February 1998, 160(4): 1627-1637), is withdrawn.

Response to Arguments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5, 8, 10, 12, 24, and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Maurer et al (Digestive Diseases and Sciences, 43(12): 2641-2648) in view of Macpherson et al (Proceedings of the American Association for Cancer Research Annual Meeting, 3/02, 43:407-408) and Chao et al (J Exp Med, September 1995, 182(3): 821-828), for the reasons stated in the Office Action of 5/23/08 and for the reasons set-forth below.

Maurer et al teaches a process comprising measuring the level of mRNA encoding Bax by detecting expression of an effector or marker gene expressing the pro-apoptotic Bax protein in a colorectal cancer cell from a subject having colorectal cancer, comprising detecting mRNA transcripts, wherein a probe or primer is used to detect the expression of the Bax gene, comprising contacting a nucleotide probe for said effector or marker gene with a biological sample to be analyzed for a time and under conditions suitable for hybridization to occur and detecting hybridization (see Figure 2, in particular). Maurer et al further teaches expression of the BAX gene varies in colorectal cancer cells (see Figure 2, in particular).

Maurer et al does not specifically teach methods comprising determining the level of expression of BAX gene in cancer cells obtained from a patient and comparing

the level with the level measured in a corresponding control sample of cells not resistant to oxaliplatin. However, these deficiencies are made up in the teachings of Macpherson et al and Chao et al.

Macpherson et al teaches reduced expression of Bcl-xl in colon cancer cells results in an enhanced apoptotic response to oxaliplatin (see abstract).

Chao et al teaches Bcl-xl functions as a repressor of apoptosis by heterodimerizing with and inhibiting pro-apoptotic BAX (page 821 and page 826, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to perform a method of detecting resistance of a cancer cell to oxaliplatin treatment by determine the level of expression of BAX gene in cancer cells obtained from the patient and comparing the level with the level measured in a corresponding control sample of cells not resistant to oxaliplatin when performing the method of Maurer et al because Macpherson et al teaches reduced expression of Bcl-xl, a repressor of apoptosis that functions by inhibiting BAX (see pages 821 and 826 of Chao et al), in colon cancer cells results in an enhanced apoptotic response to oxaliplatin (see abstract of Macpherson et al). Therefore, colorectal cancer cells with less BAX expression detected in the method of Maurer et al would be expected to be more resistant to oxaliplatin than cells with higher levels of BAX expression because apoptosis of colorectal cancer cells by oxaliplatin has been shown to be controlled by a Bcl-xl mediated pathway, the expression level of a member of the Bcl-xl mediated apoptotic pathway (Bcl-xl) has been shown to modulate the Bcl-xl mediated apoptotic

pathway in colorectal cells in response to oxaliplatin, and BAX is a pro-apoptotic molecule that is repressed by Bcl-xl. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for performing a method of detecting resistance of a cancer cell to oxaliplatin treatment by determine the level of expression of BAX gene in cancer cells obtained from the patient and comparing the level with the level measured in a corresponding control sample of cells not resistant to oxaliplatin when performing the method of Maurer et al because Macpherson et al teaches reduced expression of Bcl-xl, a repressor of apoptosis that functions by inhibiting BAX (see pages 821 and 826 of Chao et al), in colon cancer cells results in an enhanced apoptotic response to oxaliplatin (see abstract of Macpherson et al). Therefore, colorectal cancer cells with less BAX expression detected in the method of Maurer et al would be expected to be more resistant to oxaliplatin than cells with higher levels of BAX expression because apoptosis of colorectal cancer cells by oxaliplatin has been shown to be controlled by a Bcl-xl mediated pathway, the expression level of a member of the Bcl-xl mediated apoptotic pathway (Bcl-xl) has been shown to modulate the Bcl-xl mediated apoptotic pathway in colorectal cells in response to oxaliplatin, and BAX is a pro-apoptotic molecule that is repressed by Bcl-xl. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

In the Reply of 11/24/08, Applicant argues that Macpherson does not teach or suggest comparing the level of expression of the gene encoding Bcl-xl in tumor and control cells to determine the degree of oxaliplatin resistance. Applicant further argues

that Chao is unconcerned with comparing Bax and Bcl expression between cancer and control cells and states that Chao focuses on the parameter of heterodimerization of Bcl-2 or of Bax. Applicant further states that in view of Chao, the person of ordinary skill would have used the ratio of the pair Bcl-2/Bax compared to unbound Bax than the level of Bax expression alone as oxaliplatin resistance marker in cancer cells. Applicant further argues that none of the cited documents suggest that in cancer cells, the level of Bax (or Bak) taken alone is indicative of oxaliplatin resistance.

The amendments to the claims and the arguments found in the Reply of 11/24/08 have been carefully considered, but are not deemed persuasive. In regard to the arguments that Macpherson does not teach or suggest comparing the level of expression of the gene encoding Bcl-xl in tumor and control cells to determine the degree of oxaliplatin resistance and that Chao is unconcerned with comparing Bax and Bcl expression between cancer and control cells, such a comparison is obvious in view of the references cited above. As stated above, one of ordinary skill in the art at the time the invention was made would have been motivated to perform a method of detecting resistance of a cancer cell to oxaliplatin treatment by determine the level of expression of BAX gene in cancer cells obtained from the patient and comparing the level with the level measured in a corresponding control sample of cells not resistant to oxaliplatin when performing the method of Maurer et al because Macpherson et al teaches reduced expression of Bcl-xl, a repressor of apoptosis that functions by inhibiting BAX (see pages 821 and 826 of Chao et al), in colon cancer cells results in an enhanced apoptotic response to oxaliplatin (see abstract of Macpherson et al).

Therefore, colorectal cancer cells with less BAX expression detected in the method of Maurer et al would be expected to be more resistant to oxaliplatin than cells with higher levels of BAX expression because apoptosis of colorectal cancer cells by oxaliplatin has been shown to be controlled by a Bcl-xl mediated pathway, the expression level of a member of the Bcl-xl mediated apoptotic pathway (Bcl-xl) has been shown to modulate the Bcl-xl mediated apoptotic pathway in colorectal cells in response to oxaliplatin, and BAX is a pro-apoptotic molecule that is repressed by Bcl-xl.

In regards to the statement that in view of Chao, the person of ordinary skill would have used the ratio of the pair Bcl-2/Bax compared to unbound Bax than the level of Bax expression alone as oxaliplatin resistance marker in cancer cells, a method comprising determining the ratio of the pair Bcl-2/Bax as compared to unbound Bax in cancer and oxaliplatin resistant cells requires detecting the expression of Bax in cancer and oxaliplatin resistant cells and comparing expression of Bax in cancer and oxaliplatin resistant cells. Such a method anticipates the claims.

In regards to the argument that none of the cited documents suggest that in the level of Bax (or Bak) taken alone is indicative of oxaliplatin resistance, Applicant is arguing limitations not recited in the claims. The claims do not limit one to only use the level of Bax or Bak to determine oxaliplatin resistance. Rather, the claims are drawn to methods "comprising" using the level of Bax or Bak to determine oxaliplatin resistance.

New Rejections Necessitated by Amendments

Claims 1, 2, 5, 8, 10-12, 24, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maurer et al (Digestive Diseases and Sciences, 43(12): 2641-2648) in view of Macpherson et al (Proceedings of the American Association for Cancer Research Annual Meeting, 3/02, 43:407-408) and Chao et al (J Exp Med, September 1995, 182(3): 821-828) as applied to claims 1, 2, 5, 8, 10, 12, 24, and 27 above, and further in view of Aggarwal et al (J Immunol, February 1998, 160(4): 1627-1637).

The combined teaching Maurer et al, Macpheron et al, and Chao et al are discussed above.

The combined teachings of Maurer et al, Macpheron et al, and Chao et al do not specifically teach a method comprising obtaining a cDNA from the RNA of the biological sample and amplifying the cDNA using at least one primer for amplification of BAX. However, this deficiency is made up in the teachings of Aggarwal et al.

Aggarwal et al teaches a quantitative PCR method comprising obtaining a cDNA from RNA of a biological sample and amplifying the cDNA using at least one primer for amplification of BAX (Figure 7, in particular).

One of ordinary skill in the art at the time the invention was made would have been motivated to use a quantitative PCR method comprising obtaining a cDNA from RNA of a biological sample and amplifying the cDNA using at least one primer for amplification of BAX when detecting the expression of BAX in the combined method of Maurer et al, Macpheron et al, and Chao et al because the quantitative PCR method of Aggarwal et al would provide quantitative results for determining BAX expression in the combined method of Maurer et al, Macpheron et al, and Chao et al. One of ordinary

skill in the art at the time the invention was made would have had a reasonable expectation of success for using a quantitative PCR method comprising obtaining a cDNA from RNA of a biological sample and amplifying the cDNA using at least one primer for amplification of BAX when detecting the expression of BAX in the combined method of Maurer et al, Macpheron et al, and Chao et al because Aggarwal et al teaches primers that amplify BAX cDNA and methods of using said primers to amplify BAX cDNA (page 1628, in particular). Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Summary

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN E. AEDER whose telephone number is (571)272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sean E Aeder/
Examiner, Art Unit 1642

/MISOOK YU/

Primary Examiner, Art Unit 1642